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Risk-Reducing Strategies for Ovarian Cancer in *BRCA* Mutation Carriers: A Balancing Act

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Ovarian cancer • *BRCA* • Bilateral salpingo-oophorectomy • Salpingectomy with delayed oophorectomy • Screening • Chemoprevention

Abstract

Objective. The objective of this study was to review the role of bilateral salpingo-oophorectomy in *BRCA* mutation (m*BRCA*) carriers and alternative interventions in risk reduction of ovarian cancer (OC).

Materials and Methods. A systematic review using PubMed, MEDLINE, EMBASE, and the Cochrane library was conducted to identify studies of different strategies to prevent OC in m*BRCA* carriers, including bilateral salpingo-oophorectomy, prophylactic salpingectomy with delayed oophorectomy, intensive surveillance, and chemoprevention.

Results. Risk-reducing bilateral salpingo-oophorectomy is an effective intervention, but its associated morbidity is substantial and seems to curtail uptake rates among the target population. Although there is much interest and a strong theoretical basis for salpingectomy with delayed oophorectomy, data on its clinical application are scarce with regard to screening, the use of an algorithmic protocol has recently shown favorable albeit indefinite results in average-risk postmenopausal women. Its incorporation into studies focused on high-risk women might help solidify a future role for screening as a bridge to surgery. The use of oral contraceptives for chemoprevention is well supported by epidemiologic studies. However, there is a lack of evidence for advocating any of the other agents proposed for this purpose, including nonsteroidal anti-inflammatory drugs, vitamin D, and retinoids.

Conclusion. Further studies are needed before salpingectomy with delayed oophorectomy or intensive surveillance can be offered as acceptable, less morbid alternatives to upfront oophorectomy for m*BRCA* carriers. ***The Oncologist*** 2017;22:450–459

Implications for Practice: Risk-reducing bilateral salpingo-oophorectomy is currently the most effective method for reducing the risk of ovarian cancer in *BRCA* mutation (m*BRCA*) carriers. Unfortunately, it is associated with significant short- and long-term morbidity, stemming from reduced circulating estrogen. In recent years, much research has been devoted to evaluating less morbid alternatives, especially multimodal cancer screening and prophylactic salpingectomy with delayed oophorectomy. This review describes the present state of the art, with the aim of informing the counseling provided to m*BRCA* carriers on this complicated issue and encouraging additional research to facilitate the incorporation of such alternatives into routine practice.

Introduction

Ovarian cancer (OC) is the seventh leading cause of cancer-related death among women worldwide [1]. Incidence rates are highest in developed countries, where it is the second most common gynecologic malignancy and the most lethal [1, 2]. Family history of breast and OC is the most significant risk factor. Hereditary breast/OC syndrome, characterized by a family history of multiple relatives affected by early-onset breast and/or OC, is implicated in approximately 10% of OC cases, the majority of which are due to a deleterious germline mutation in the *BRCA*1 or *BRCA*2 tumor-suppressor genes [3]. Based on three key studies (two meta-analyses and one prospective cohort study), the cumulative risk of OC by age 70 ranges between 35%–45% and 15%–18% for *BRCA*1 and *BRCA*2, respectively [4–6].

The mainstay of OC prevention in these patients, risk-reducing bilateral salpingo-oophorectomy (rrBSO), is recommended at the age of 35–40 or after completion of childbearing [7]. Although proven to be an effective strategy, the induction of premature menopause and lifelong health risks owing to estrogen deficiency are significant [8]. Therefore, any

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alternative strategy that could delay or obviate oophorectomy altogether while still providing cancer risk reduction would be of much value. In this review, we summarize the efficacy and pitfalls of rrBSO, its effect on quality of life (QOL), and the spectrum of current alternative surgical and nonsurgical preventive strategies.

Methods

A systematic review using MEDLINE, EMBASE, and the Cochrane library was conducted. In addition, PubMed was searched for relevant randomized trials, scientific articles, and other high-quality studies, such as meta-analyses, between January 1, 1995, and October 30, 2016. Search terms included "ovarian cancer," "*BRCA*," "risk reduction," "bilateral salpingo-oophorectomy," "salpingectomy with delayed oophorectomy," "fimbriectomy," "screening," "chemoprevention," and "hormone replacement therapy." References identified from relevant articles were also searched. No language restrictions were included. As a secondary analysis and review of published data, the study was exempt from institutional review board approval.

Risk Reduction Benefits of Bilateral Salpingo-Oophorectomy

Ovarian/Fallopian Tube Cancer

rrBSO substantially reduces the risk of ovarian and fallopian tube cancer in m*BRCA* carriers (Table 1). In 2009, a meta-analysis of three previous studies with over 2,840 participants in total showed an 80% reduction in the incidence of these cancers in m*BRCA* carriers who had undergone rrBSO versus those who had not (95% confidence interval [CI] 0.12–0.39) [9]. Two large subsequent prospective studies showed a similar risk reduction while also demonstrating a substantial reduction in OC-specific mortality (hazard ratio [HR] = 0.25, 95% CI 0.08–0.75) and all-cause mortality to age 70 years (HR = 0.31; 95% CI 0.26–0.39) [10, 11].

There is some evidence to suggest that the magnitude of protection provided against OC might differ by mutation type. This was demonstrated by Marchetti et al., who performed a subgroup analysis of over 4,310 m*BRCA* carriers for a mean follow-up period of 4.8 years and showed that although the post-procedural hazard ratio for OC was 0.20 in *BRCA*1 carriers ($p < .00001$), there was no demonstrable benefit in *BRCA*2 patients (HR = 0.21; $p = .22$) [12]. This effect may be attributable to the increased risk of OC associated with a *BRCA*1 mutation compared with a *BRCA*2 mutation, as well as to a smaller sample size of *BRCA*2 subjects. At this time, the data do not merit reconsidering rrBSO as the standard of care for all m*BRCA* carriers regardless of subtype.

Breast Cancer

Numerous studies have demonstrated an approximate 50% reduction in breast cancer (BC) incidence following rrBSO when performed prior to the onset of menopause [13–18]. For example, one case-control study matched 1,439 m*BRCA* carriers affected by BC with 1,866 unaffected carriers to estimate the odds ratio (OR) associated with rrBSO [16]. Oophorectomy was associated with a 57% reduction in BC risk in *BRCA*1 carriers (unadjusted OR = 0.43; $p = .00006$) and a 46% reduction in *BRCA*2 carriers (OR = 0.57; $p = .11$). The magnitude of

Table 1. Estimated HR for OC incidence, BC incidence, and all-cause mortality associated with risk-reducing bilateral salpingo-oophorectomy

References	*BRCA*1/2, HR (95% CI)			*BRCA*1, HR (95% CI)			*BRCA*2, HR (95% CI)		
	OC	BC	All-cause mortality	OC	BC	All-cause mortality	OC	BC	All-cause mortality
Rebbeck et al. [9]	0.21 (0.12–0.39)	0.49 (0.37–0.65)	n/a	n/a	0.47 (0.35–0.64)	n/a	n/a	0.47 (0.26–0.84)	n/a
Domchek et al. [10]	.28 (0.12–0.69)[a] 0.14 (0.04–0.59)[b]	0.54 (0.37–0.79)[a] 1.00 (0.56–1.77)[b]	0.45 (0.21–0.95)[a] 0.30 (0.17–0.52)[b]	0.31 (0.12–0.82)[a] 0.15 (0.04–0.63)[b]	0.63 (0.41–0.96)[a] 1.01 (0.54–1.89)[b]	0.52 (0.24–1.14)[a] 0.26 (0.13–0.52)[b]	No cancer events	0.36 (0.16–0.82)[a] 1.11 (0.31–3.98)[b]	No Deaths 0.45 (0.17–1.16)[b]
Finch et al. [11]	0.20 (0.13–0.30)	n/a	0.23 (0.13–0.39)[a] 0.32 (0.26–0.39)[b]	n/a	n/a	0.21 (0.12–0.37)[a] 0.31 (0.24–0.39)[b]	n/a	n/a	0.67 (0.08–5.35)[a] 0.34 (0.22–0.52)[b]
Marchetti et al. [12]	0.19 (0.13–0.27)	n/a	0.29 (0.19–0.46)[a] 0.32 (0.26–0.39)[b]	0.20 (0.12–0.32)	n/a	0.31 (0.26–0.38)	0.21 (0.02–1.91)	n/a	0.36 (0.25–0.52)

[a]No history of breast cancer.
[b]History of prior breast cancer.
Abbreviations: BC, breast cancer; CI, confidence interval; HR, hazard ratio; n/a, not available; OC, ovarian cancer.

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protection fell dramatically with increasing age, with an OR of 0.36 if performed at age ≤40, 0.50 at age 40–50, and a statistically insignificant risk reduction if performed after age 50.

However, two recent prospective studies suggest that the magnitude of BC risk reduction after rrBSO might have been overestimated. In 2016, Kotsopoulos et al. published the largest prospective analysis to date on this issue, with 3,720 participants and a mean follow-up period of 5.6 years [19]. In their overall analysis, the authors found no statistically significant association between rrBSO and BC risk. The study did report on a statistically significant protective effect in *BRCA*2 carriers prior to age 50 (HR = 0.18; 95% CI 0.05–0.63; $p = .007$), but this was based on three cases only. Similarly, a prospective study from the Netherlands, which aimed to eliminate lead-time bias by accounting for person-time, found no protective effect of rrBSO on BC risk (HR = 1.09; 95% CI 0.67–1.77) [20].

Primary Peritoneal Carcinoma

The efficacy of rrBSO does not reduce the risk of developing primary peritoneal carcinoma (PPC), an entity of identical histology to OC but with no or minimal involvement of the ovaries [21]. The risk for PPC after rrBSO has been reported in the range of 0.8%–10.7%, with one large prospective study of 1,828 *BRCA*1/2 carriers estimating a 4.2% percent risk in a 20-year period following the procedure. The risk appears to be greater in *BRCA*1 carriers [22, 23].

Morbidity Associated with rrBSO

m*BRCA* carriers who undergo rrBSO and the ensuing surgical menopause are affected by the immediate compromises to QOL and a myriad of long-term health risks stemming from hypoestrogenism. In the short term, climacteric symptoms and sexual dysfunction have been well documented [24–28]. For instance, a prospective study of 114 m*BRCA* carriers utilized the Menopause-Specific Quality of Life Intervention questionnaire to show that women who were premenopausal at the time of rrBSO experienced a significant worsening of hot flashes, night sweats, and sweating 1 year after surgery ($p < .0001$), reaching levels comparable to women who are 2–7 years postmenopausal [23]. In a more recent study from Norway, 294 women who underwent rrBSO were questioned about various measures of sexual activity (i.e., frequency, interest in sex), sexual pleasure (e.g., enjoyment, satisfaction), and discomfort (e.g., vaginal dryness, dyspareunia). These were then compared with a random sampling of women from the general population, with the resulting observations that women in the rrBSO group experienced less sexual pleasure (10.5 versus 11.9, $p = .009$), more discomfort (1.9 versus 0.83, $p < .001$), and less frequent sex than did the controls [28].

The long-term consequences for women who have undergone rrBSO before menopause include an increased risk of coronary heart disease (CHD), hyperlipidemia, obstructive lung disease, cognitive dysfunction, mental health problems, and osteoporosis [29]. In addition, they are subject to an accelerated accumulation rate of these and many other chronic conditions such as diabetes, stroke, and arthritis. With regards to CHD, the Nurse's Health Study included almost 30,000 women who had undergone hysterectomy for benign indications, of which 55.6% included bilateral oophorectomy [30]. A follow-up period of 24 years showed that, compared with ovarian conservation, bilateral oophorectomy at the time of hysterectomy was associated with a higher risk of fatal and nonfatal CHD (HR = 1.17; 95% CI 1.0–1.52).

Most of the data about cognitive dysfunction and mental health after oophorectomy come from analyses based on the Mayo Clinic Cohort Study of Oophorectomy and Aging [31–33]. In this cohort, unilateral or bilateral oophorectomy performed prior to menopause was associated with an increased risk of cognitive impairment or dementia (HR = 1.46; 95% CI 1.13–1.90), depressive symptoms (HR = 1.54; 95% CI 1.04–2.26), anxiety symptoms (HR = 2.29; 95% CI 1.33–3.95), and parkinsonism (HR = 1.68; 95% CI 1.06–2.67; $p = .03$). All of these effects were found to increase with younger age at oophorectomy and were independent of the indication for surgery.

Hormonal Therapy After rrBSO

Administering hormonal replacement therapy (HRT) to alleviate post-rrBSO symptoms is an attractive option. However, its use by women who are already at increased risk for BC is counterintuitive and merits careful consideration. Due to inconclusive evidence regarding an increased risk of endometrial cancer in m*BRCA* carriers, the current standard for rrBSO does not include hysterectomy [34]. Therefore, the decision on which type of HRT to administer depends largely on whether or not the uterus has been retained. In women who have retained their uterus, progesterone must be combined with estrogen for HRT to prevent stimulation of the endometrial lining and endometrial neoplasia. This presents a challenge to caregivers, as data from the Women's Health Initiative showed a significant increased risk of BC from the estrogen-progesterone combination of Prempro compared with placebo and also compared with estrogen alone in postmenopausal women with no prior history of BC (HR = 1.28; 95% CI 1.11–1.48) [35–39]. Still, the existing, if limited, data available from observational studies conducted specifically in m*BRCA* carriers suggest that HRT is safe following rrBSO and does not negate its protective benefit against BC [36–38].

Beyond the question of safety, it appears that HRT only partially mitigates climacteric symptoms experienced after oophorectomy and does not alleviate sexual discomfort. In a cross-sectional observational study, Madalinska et al. compared 164 women at high risk of OC who underwent rrBSO with 286 similarly high-risk women who opted for routine screening [26]. In the rrBSO group, 77 women were prescribed HRT and 87 were not. A comparison of the three groups by way of questionnaire showed that although post-rrBSO women who were prescribed HRT had fewer vasomotor symptoms than post-rrBSO women without HRT ($p < .05$), symptom levels were still significantly above those in the routine screening arm ($p < .01$). Worse still, HRT did not alleviate sexual discomfort after rrBSO, with HRT users and non-users demonstrating comparable levels of sexual discomfort and significantly more vaginal dryness and dyspareunia compared with the screening arm ($p < .01$). Decreased libido, which in one study has been shown to affect 34% of oophorectomized women compared with 26% of controls, also may persist despite estrogen therapy [28, 40].

Consequences on Uptake of rrBSO

The health implications of rrBSO seem to have a demonstrable effect on uptake rates among m*BRCA* carriers. Choosing rrBSO

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ranges from as low as 29% in one study after a 3-year follow-up period [40] to a maximum of 75% after a 10-year follow-up period in a recent study from Denmark [40, 42]. Furthermore, analysis of average timespans from the time of genetic testing to surgery shows that some women delay the procedure for several years [43]. Importantly, the two major demographic predictors of rrBSO are older age and completion of childbearing, suggesting that concerns regarding surgical menopause are a deterrent to more widespread adoption [44].

Alternatives to rrBSO

The two main avenues currently explored as alternatives to rrBSO are (a) prophylactic salpingectomy with delayed oophorectomy (PSDO) and (b) intensive screening. Chemoprevention, a third area of interest, includes the use of oral contraceptive pills (OCP)—currently recommended as a reasonable adjunct measure—and other candidate agents [45–47].

PSDO

A significant proportion of carcinomas identified incidentally at rrBSO are localized to the fallopian tube rather than the ovary [48–51]. These lesions are often found while still confined to the tubal epithelium (serous tubal intraepithelial carcinoma [STIC]), and their reported prevalence varies considerably, reaching up to 100% of all occult lesions identified in one series [52]. Using the sectioning and extensively examining of the fimbriated end and endometrium (SEE-FIM) protocol, the fimbria has been pinpointed as the most commonly involved site [53].

Given that the fallopian tube is a frequent site of early carcinoma in m*BRCA* patients, a paradigm-shifting hypothesis has emerged that nominates STIC as a probable precursor lesion for all subtypes of pelvic serous carcinoma, making it a target for early detection and prevention [54–56].

> Prophylactic salpingectomy after the completion of childbearing with PSDO is increasingly being suggested as a less morbid alternative to rrBSO in m*BRCA* carriers.

Consequently, prophylactic salpingectomy after the completion of childbearing with PSDO is increasingly being suggested as a less morbid alternative to rrBSO in m*BRCA* carriers [57–59]. It is argued that salpingectomy might confer sufficient risk reduction, until oophorectomy can be completed. Support for this hypothesis is drawn from epidemiological data showing that both tubal ligation and salpingectomy are associated with a reduced risk for both sporadic and hereditary OC [60, 61]. On the other hand, concerns have been raised about the adequacy of complete surgical separation of the fimbria from the surface of the ovary [62].

Notably, the tubal origin hypothesis has also led expert groups in Canada and Germany to encourage general gynecologists to perform opportunistic salpingectomy in low-risk women either at the time of hysterectomy performed for benign indications or as an alternative to tubal ligation for sterilization [63, 64]. The impact of this practice on risk reduction in the general population has not been determined.

Estimated Risk/Benefit Ratio and Surgical Safety

There are currently no data on the clinico-pathological outcomes of PSDO in m*BRCA* carriers. However, several indirect analyses have shed light on some aspects of this approach. In 2013, Kwon et al. used a Markov Monte Carlo simulation model to compare three possible interventions in m*BRCA* carriers: bilateral salpingectomy at age 40, rrBSO at age 40, and bilateral salpingectomy at age 40 followed by bilateral oophorectomy 10 years later [65]. Investigated outcomes included cost, the number of future OCs and BCs, the number of cardiovascular deaths attributed to premature menopause, and life expectancy evaluated as both years-of-life expectancy and quality-adjusted life expectancy. In this analysis, rrBSO carried the lowest cost, the greatest risk reduction for OC and BC, and the highest life expectancy. However, PSDO yielded the highest quality-adjusted life expectancy, assuming that patients who underwent rrBSO were not prescribed HRT.

More recently, Harmsen and colleagues modeled data from previous studies to estimate the cumulative risks of OC for rrBSO versus PSDO in *BRCA*+ carriers [66]. The authors constructed two hypothetical scenarios for the risk reduction provided by PSDO: a best-case scenario (65% risk-reduction rate) and a worst-case scenario (0%). In the best-case scenario, risk-reduction benefits were comparable between the two approaches. In the worst-case scenario for *BRCA*1 carriers, performing a non-protective salpingectomy at age 40 and delaying oophorectomy by 5 years from age 40 to age 45 raised the cumulative risk point estimate by 2.3 (from 1.8% to 4.1%). In the similar scenario for *BRCA*2, delaying oophorectomy by 5 years from age 45 to age 50 raised the point estimate by 1.2 (from 0.6% to 1.8%). The authors concluded that PSDO may be offered as a viable alternative to rrBSO in the setting of a clinical trial, with the above risk estimates serving to facilitate a personalized decision-making process that takes mutation subtype and current age into account.

Regarding surgical safety, Leblanc and colleagues conducted a feasibility study of a novel procedure called "radical fimbriectomy" [67]. In this procedure, the fallopian tube is resected in its entirety along with its attachment to the ovary at the fimbrio-ovarian junction. The ovary is grasped using atraumatic forceps, divided, and then removed along the portion that is tethered to the fimbria while preserving the infundibulopelvic blood supply. A maximum of one quarter of the ovarian volume is removed along with the fimbria. Fourteen m*BRCA* carriers underwent this procedure as part of rrBSO, with the authors concluding that "radical fimbriectomy" could be safely offered to m*BRCA* carriers [67]. A prospective trial is currently underway to assess the morbidity of this technique, the rate of occult lesions in the extracted specimens, the impact on BC incidence, and compliance levels in completing the interval oophorectomy [68]. Finally, prophylactic salpingectomy via single-port access laparoscopy and a diode laser has been described as a safe surgical approach in one case report of a *BRCA*1 mutation carrier [69]. The authors suggest that a diode laser might be superior to CO_2 or argon beam laser for this procedure as it causes less thermal distortion to the extract fallopian tube, thus ensuring minimal interference to the subsequent pathological examination necessary for detecting occult carcinoma. Current Society for Gynecologic Oncology (SGO) guidelines recognize

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the efforts outlined above but stress that due to lack of evidence at this time, PSDO should only be offered to those reluctant to undergo rrBSO at the recommended age and not as an upfront substitute [70].

Patients' and Physicians' Attitudes

Studies have shown an interest in PSDO among a third of m*BRCA* carriers and 60% of caregivers, with both groups citing the avoidance of premature menopause as the key facilitator [71–73]. On the other hand, many significant barriers to adoption must be addressed. Among patients, the main concerns stem from awareness of the seriousness of OC, uncertainty about the risk reduction provided by PSDO, a family history of OC, and personal history of BC [73]. Among caregivers, including gynecologic oncologists and geneticists, the main deterrents are scarcity of data on the level of benefit (83%), increased morbidity from adding a second procedure (79%), loss of BC risk reduction (68%), the need for long-term follow-up (61%), and possible failure by some women to complete the interval oophorectomy (66%) [72].

Ongoing Clinical Studies

Several prospective studies are currently underway to further elucidate the clinical utility of PSDO. In the Netherlands, a multicenter nonrandomized study ("TUBA") will examine how bilateral salpingectomy after completion of childbearing with oophorectomy at age 40–50 compares with upfront rrBSO in terms of menopause-related QOL and OC incidence [74]. At the MD Anderson Cancer Center in the U.S., a nonrandomized trial is aimed at comparing three patient-selected interventions: (a) multimodal screening (MMS), including CA-125 and TVUS; (b) PSDO with oophorectomy 3 years after salpingectomy; and (c) rrBSO. The primary outcome is compliance with PSDO [75]. Finally, a nonrandomized two-arm trial called Women choosing Interval Salpingectomy with Delayed Oophorectomy to postpone Menopause ("WISDOM") is under development, with the purpose of evaluating changes in sexual function in women undergoing PSDO versus rrBSO [76].

Intensive Screening

Lack of Clear Benefit for Screening in High-Risk Women

The SGO and the National Comprehensive Cancer Network have recommended MMS for OC in m*BRCA* carriers while simultaneously emphasizing that it has not been shown to reduce mortality [3, 77]. More recently, in September 2016, the U.S. Food and Drug Administration issued a warning against the use of commercially available OC screening tests, such as CA 125 and HE-4, on the grounds of insufficient evidence, citing concern that their use may delay effective preventive treatments for high-risk women [78]. Indeed, the accumulated data from prospective studies demonstrate no clear benefit for screening in terms of survival or down-staging of detected cases.

For example, Hermsen et al. reported on a cohort of 888 m*BRCA* carriers who underwent annual surveillance with CA-125 measurements and transvaginal ultrasound (TVUS) for a total of 1,473 women-years [79]. Ten incident cancers were detected during the follow-up period, of which eight cases were diagnosed at Stage III, demonstrating a failure to facilitate down-staging. Furthermore, five out of the ten cases were interval cases, diagnosed in women who received a negative screening result within 3–10 months prior to diagnosis. A later study by Evans et al. evaluated the impact of annual screening with TVUS and CA-125 on survival rates in 981 *BRCA* carriers [80]. Ten-year survival of 49 diagnosed cases was 36% (95% CI 27%–45%), which is not significantly lower than what would be expected in an unscreened population. In addition, there was little evidence for down-staging from the prevalent round, with approximately 65% of cases in both rounds diagnosed at stages III–IV.

Slightly more encouraging results come from the largest screening study of high-risk women, the United Kingdom Familial Ovarian Cancer Screen Study [81]. This study included 3,563 women at high risk for OC who were screened annually with TVUS + CA-125 for a mean follow-up period of 3.2 years [81]. Impact on mortality was not one of the investigated outcomes, but the study yielded two favorable observations. First, the reported negative predictive value was 99.9% (95% CI 99.8–100), suggesting that a negative screen result might be used reliably as an aid in the decision to delay rrBSO for another year. Second, screening in the year before diagnosis was associated with a lower chance of being diagnosed at stage IIIC and above, suggesting that strict adherence to the surveillance schedule, coupled with a higher frequency of screening sessions, might eventually lead to down-staging of incident cases.

Enhanced Screening with the Risk of Ovarian Cancer Algorithm

The Risk of Ovarian Cancer Algorithm (ROCA), which triages patients to various screening frequencies based on longitudinal changes in CA-125 levels, might drive improvements to screening. In December 2015, results from the Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) were published to much debate [82]. This randomized trial compared ROCA-based MMS and TVUS against no intervention in postmenopausal women, and primary analysis showed insignificant mortality reductions for MMS (15% reduction; 95% CI −3–30; $p = .10$) and TVUS (11% reduction; 95% CI −7–27; $p = -.21$). However, a secondary analysis in which the authors excluded either prevalent cases or deaths in the first 7 years after randomization showed a 20% average mortality reduction in the MMS arm (95% CI −2–40; $p = .021$). It should be noted that the merits of this secondary analysis have been disputed, with an additional potential bias pointed out between the MMS and no-screening arms in terms of the number of CA-125 measurements taken [83].

The incorporation of ROCA into two currently ongoing trials focused on high-risk women will perhaps help clarify a role for screening as a reasonable alternative to women wishing to delay rrBSO. One of the two studies is the Gynecologic Oncology Group Protocol 199, a prospective, nonrandomized trial designed to determine the impact of rrBSO versus ROCA-based screening on OC and BC incidence [81, 84]. The study has completed 5 years of prospective follow-up in 2011 and is now in the analysis phase.

Chemoprevention

OCP

OCP use reduces the risk of OC in the general population. For example, in 2008 a reanalysis of data from 45 epidemiological studies including 23,257 women with OC and 87,303 controls showed that for every 5 years of OCP use, the overall relative

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Table 2. Level of evidence for ovarian cancer risk-reducing interventions in *BRCA* mutational Carriers (m*BRCA*)

Intervention	Estimated risk-reduction provided	Level of evidence [104]	Grade practice recommendations [105]
rrBSO	~80% [9–11]	Level 2 (Observational studies with dramatic effect)	Grade A = strong recommendation
Oral contraceptives	50% [86]	Level 4 (Case-control studies)	Grade B = Recommendation
Screening [82]	NPV = 99.9% [81] Adherence to screening associated with a lower chance of being diagnosed at stage 3C and above	Level 4; graded down from Level 3 due to inconsistencies with other studies (Nonrandomized controlled cohort)	Option
PSDO	Risk-reduction comparable with rrBSO [66]; Offers higher quality-adjusted life expectancy compared with rrBSO [65]	Level 5 (mechanism-based reasoning)	Option May be considered for carriers reluctant to undergo rrBSO, preferably in the context of a clinical trial
Chemoprevention with NSAIDs, vitamin D, or fenretinide (4-HPR)	No data on risk-reduction in m*BRCA* carriers	Level 5 (mechanism-based reasoning)	Option

Abbreviations: m*BRCA*, *BRCA* mutation; NSAIDs, nonsteroidal anti-inflammatory drugs; PSDO, prophylactic salpingectomy with delayed oophorectomy; rrBSO, risk-reducing bilateral salpingo-oophorectomy.

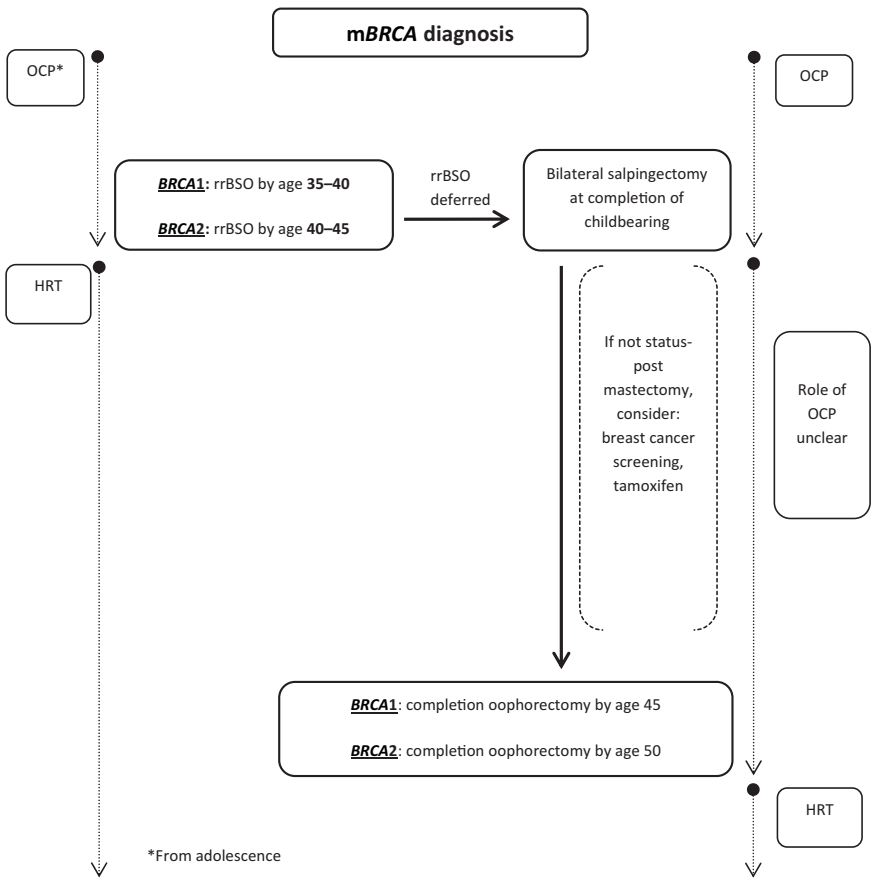

Figure 1. Decision flowchart for rrBSO versus PSDO.
Abbreviations: HRT, hormonal replacement therapy; m*BRCA*, BRCA mutation; OCP, oral contraceptive pills; PSDO, prophylactic salpingectomy with delayed oophorectomy; rrBSO, risk-reducing bilateral salpingo-oophorectomy.

risk of OC decreases by 20% (95% CI 18%–23%; $p < .0001$), with the risk halving after 15 years [85]. The data also showed that the duration of protection lasts for more than 30 years after discontinuing usage.

The same protective effect has been studied and shown to persist in m*BRCA* carriers. As such, OCP are advocated as a preventive intervention for this patient group [7]. For instance, Iodice et al. performed a meta-analysis of five studies (either

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case-control or retrospective cohort) and showed a significantly reduced risk of OC in OCP users harboring an m*BRCA* (RR = 0.50; 95% CI 0.33–0.75), which is proportional to the duration of use and is independent of mutation subtype [86].

Because OCP have been shown to modestly increase the risk of BC in the general population, there is a similar theoretical concern regarding m*BRCA* carriers [87]. Investigations into the matter have produced conflicting evidence. The meta-analysis by Iodice et al. reported no such association in women using post-1975 contraceptive formulations (with reduced estrogen concentrations) or in the first 10 years following discontinuation of use. In contrast, a more recent meta-analysis from 2013 did in fact demonstrate a trend towards increased risk of BC under contraceptive use in both *BRCA*1 (OR = 1.19; 95% CI 0.92–1.55) and *BRCA*2 carriers (OR = 1.21; 95% CI 0.93–1.58) and to a higher extent than reported for the general population (OR ≈ 1.08) [88]. However, this did not reach statistical significance.

Other Candidates for Chemoprevention

There is some evidence to suggest that pelvic inflammatory disease may elevate the risk of OC, especially in women with recurrent episodes [89, 90]. It follows then that anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) might have a protective role to play, similar to the effect demonstrated in colorectal cancer and other solid malignancies [91, 92].

Aspirin has been shown to inhibit the growth of OC cells at the molecular level, but data concerning NSAIDs' clinical utility in this context are inconsistent [93]. Out of three separate meta-analyses conducted in recent years, one study from 2013 failed to show a significant association between NSAIDs and OC incidence, while the other two demonstrated a moderate inverse association [94–96]. In the more recent of the two, Zhang et al. synthesized results from 8 cohort studies and 15 case-control studies to demonstrate a slight risk reduction associated with aspirin use (RR = 0.89; 95% CI 0.83–0.96), with a possible dose-response relation between frequency of use and cancer risk [96]. In addition, a pooled analysis of 12 population-based studies with a total sample size of over 10,000 subjects showed that daily low-dose aspirin (<100 mg) could reduce the risk of OC by as much as 20%–34% [97]. On the basis of this last finding, Tsoref and colleagues offered the compelling calculation that only about 8–13 m*BRCA* carriers would have to be treated in order to prevent one case of OC, which could make a strong case for recommending treatment [46].

Vitamin D has been shown to slow the progression of epithelial OC cells in preclinical studies. Furthermore, epidemiological analysis of single nucleotide polymorphisms related to vitamin D expression has shown that genetically lowered 25-hydroxyvitamin D concentrations are associated with elevated susceptibility to OC in European women.

Vitamin D has been shown to slow the progression of epithelial OC cells in preclinical studies [98, 99]. Furthermore, epidemiological analysis of single nucleotide polymorphisms related to vitamin D expression has shown that genetically lowered 25-hydroxyvitamin D concentrations are associated with elevated susceptibility to OC in European women [47]. However, data from case-control and cohort studies are inconsistent, with a systematic review of ten such studies showing no strong evidence for risk reduction and a meta-analysis of many of the same studies reporting only on a tentative risk reduction of 17% for each increase of circulating 25(OH)D by 20 ng/mL, which did not reach statistical significance ($p = .160$) [100, 101].

Finally, the antitumor properties of fenretinide (4-HPR), a synthetic vitamin A analog, have been demonstrated in in vitro and in vivo studies [102]. 4-HPR was also associated in a single randomized clinical study with a lower incidence of OC in women with prior BC, but no additional studies have provided insight on the matter since [103].

Recommendations

We present practice recommendations for each of the various risk-reduction interventions explored herein based on the level of evidence (Table 2) [104, 105]. In addition, a decision-making flowchart is proposed (Fig. 1). Genetic counseling and testing are recommended for all women affected by high-grade OC as well as unaffected women with an affected first-degree relative or several close relatives [106]. OCP are recommended from the time of diagnosis of m*BRCA* to oophorectomy. Counseling about potential side effects and contraindications to OCP should be provided to facilitate an individualized approach. *BRCA*1 mutation carriers are advised to undergo rrBSO by the age of 35–40. Based on the later age of onset of OC in *BRCA*2 carriers, some flexibility is possible as to the timing of rrBSO, which may be more suitable for women who have undergone mastectomy. The age of onset of OC in the family should also be taken into account regardless of mutation subtype. It is not unreasonable to prescribe HRT after rrBSO to women without a personal history of BC; however, additional prospective studies are required for a better understanding of the long-term risk/benefit ratio for HRT in this setting.

For those who are reluctant to undergo rrBSO at the recommended age, bilateral salpingectomy may be offered at the completion of childbearing with oophorectomy to be performed by age 45 in *BRCA*1 carriers and 50 in *BRCA*2 carriers. Because delaying oophorectomy will significantly diminish the protection against BC, mastectomy, strict BC screening, and chemoprevention with tamoxifen should be strongly considered [107]. The role of OCP in the interim period between bilateral salpingectomy and completion oophorectomy is unclear; however, in one case-control study by the Hereditary Ovarian Cancer Clinical Study Group, the combination of OCP and tubal ligation provided a larger magnitude of OC risk reduction in *BRCA*1 carriers compared with each intervention alone [108].

Conclusion

Two strategies currently being investigated might allow m*BRCA* carriers in the future to defer oophorectomy without compromising safety. With several prospective studies underway, the evaluation of PSDO has finally entered a practical phase, which will elucidate the many questions surrounding its clinical utility. As for surveillance, recent strides using algorithmic triaging in postmenopausal women, although controversial, merit further investigation in the high-risk population. Until more data are made available, rrBSO and OCP remain the only recommended

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preventive measures in m*BRCA* carriers for substantially reducing the risk of OC.

Author Contributions

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Data analysis and interpretation: Annekathryn Goodman
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Final approval of manuscript: Annekathryn Goodman

Disclosures

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For Further Reading:

Eileen E. Parkes, Richard D. Kennedy. Clinical Application of Poly(ADP-Ribose) Polymerase Inhibitors in High-Grade Serous Ovarian Cancer. ***The Oncologist*** 2016;21:586–593.

Implications for Practice:

The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib has recently received approval from the Food and Drug Administration (FDA) and European Medicines Agency (EMA), with a second agent (rucaparib) likely to be approved in the near future. However, the patient population with potential benefit from PARP inhibitors is likely wider than that of germline BRCA mutation-associated disease, and biomarkers are in development to enable the selection of patients with the potential for clinical benefit from these agents. Questions remain regarding the toxicities of PARP inhibitors, limiting the use of these agents in the prophylactic or adjuvant setting until more information is available. The indications for olaparib as indicated by the FDA and EMA are reviewed.